From: Ginsberg, Gary
To: dhattis@(b) (6) Ravi Subramaniam/DC/USEPA/US@EPA
Cc: Paul White/DC/USEPA/US@EPA; KennyCrump@email.com
Subject: RE: your perspective on NRC review
Date: 05/09/2011 01:03 AM

Hi Ravi - thanks for the invitation to review the situation with formaldehyde. The work that you and Kenny and associated others have done on this complex model is highly informative and supports the notion that with more complexity comes more opportunity for greater uncertainty when extrapolating beyond the calibration dataset. Having numerous parameters that cannot be directly measured and only calibrated against a far downstream endpoint such as basal mutation rate (calibrated against control nasal tumor rate) or formaldehyde induced increase in cell proliferation rate (calibrated against formaldehyde tumor data) is problemmatical, especially when these parameters are highly influential as you have clearly shown. It is also problematic that the Conolly et al. estimate of the fraction of the tumor response attributable to DPX vs the induction of cell proliferation has gained traction in spite of this having little empirical evidence. I think the most straightforward approach is to base the dose response on the accumulation of DPX in target tissues in relation to external dose as has been modeled most recently by EPA with justification that these DPX can be expected to have a linear response at low dose. Basal proliferation of nasal tissue in rats and humans can be expected to fix the DPX as a mutation and expand clones of initiated cells even if there is no acceleeration in these processes induced by formaldehyde at low dose. The Conolly model seems to focus on formaldehyde-induced increase in basal proliferation rate but I would imagine the basal rate will be substantial and able to move DPX towards mutation and cancer. As a high turnover epithelial tissue, the basal proliferative rate of nasal mucosa must be substantial and may be a point that could be useful as you proceed in your exploration of the low dose formaldehyde response. The other point which seems obvious to explore is the background rate of human nasal tumors as this type of data was influential in the rat model (governing basal mutation rates) and rats have very low rates of nasal carcinoma. Humans may have higher or lower background rates and this may influence the BBDR two stage model but I didn't see human background nasal tumor rates brought into the modeling.

I must confess to a rather superficial understanding of formaldehyde as I have not followed the Conolly modeling closely or the ensuing back and forth regarding the sensitivity analysis or NAS review. However, my read of all this over the past two days suggests that further justification of the alternative parameter values used in the Crump/Subramaniam papers to show that they are just as if not more reasonable than those originally used by Conolly and perhaps further exploration of certain aspects of the model (e.g., implications of high rates of basal nasal mucosa turnover at low formaldehdye dose, implications of human background rate of nasal cancer) may be sufficient to move the analysis fo Gary

From: dhattis@(b) (6) [dhattis@(b) (6)
Sent: Friday, May 06, 2011 10:54 AM
To: Subramaniam.Ravi@epamail.epa.gov; Ginsberg, Gary
Cc: White.Paul@epamail.epa.gov; KennyCrump@email.com
Subject: Re: your perspective on NRC review

Dear Ravi and Kenny,

I have now read the NRC comments in both the summary and Chapter 3. The attached annotated sections of the report contain my detailed responses and suggestions in italics. Briefly, I think the NRC report can be fairly criticized for failing to appreciate the strength of the argument that the reversibility of formaldehyde-reactant reactions requires that inhaled formaldehyde is transmitted extensively in the body at some rate, and there is no justification to adopt an implicit null hypothesis of no transmission in the absence of experimental detection of some excess above the inevitable noise by existing imperfect measurement methods. I also think it was probably unnecessary (and perhaps impolitic) for the IRIS document to make an outright rejection of the BBDR modeling framework at low doses on grounds of uncertainty. Instead, although challenging, I think you can use your extensive sensitivity analyses as the starting point for a fair and balanced analysis of the range of "not clearly incorrect" values for incremental human risks for nasal, upper respiratory, and other cancers from low dose formaldehyde exposures. Such an analysis, evaluated by both likelihood and Bayesian subjective probability methods, could also yield useful information for juxtaposing likely economic and health effects of alternative regulatory control options.

I would be happy to contribute to such efforts, although in the light of other commitments I do not have an extensive amount of time to devote to this in the next several months.

Best wishes,

Dale

-----Original Message-----
From: Subramaniam.Ravi@epamail.epa.gov
To: Gary.Ginsberg@po.state.ct.us; DHattis@(b) (6) yCrump@email.com>
Cc: White.Paul@epamail.epa.gov; Kenny Crum
Sent: Wed, May 4, 2011 12:01 pm
Subject: your perspective on NRC review

Hi Dale and Gary:
You may know that the NRC completed its review of our formaldehyde IRIS assessment recently. It was very critical of our evaluation and use of the Conolly et al (CIIT) BBDR modeling and human extrapolation of the rat nasal tumor data in our assessment. We did use the CIIT BBDR model for rats to determine a point of departure based on an internal dose metric (formaldehyde flux) and then used the human computational fluid dynamics model to translate this POD to humans. In so doing, we had rejected their BBDR model for humans. We had carried out extensive uncertainty analysis which showed their human model as too uncertain to warrant replacing EPA's baseline approach. However the NRC opined that we should have used the the BBDR model for low dose human extrapolation, asserting that it was "one of the best-developed BBDR models to date".

We are in the process of revising the document in response to NRC suggestions. In the interim, we think a short paper that clarifies our uncertainty and sensitivity analysis further would help the process. We would very much appreciate your fresh perspective on our work if you can spare the time, and to see if there is mutual interest in collaborating on such a paper.

I am attaching the following: 1) NRC review summary (see page 4,5); 2) NRC Chapter 3 (see pages 31-45)-- this has their review of the BBDR use in more detail; 3) Crump et al. (2008)--our sensitivity analysis of Conolly human model; 4) Conolly et al. (2009)-- Rory's letter to the journal critiquing our paper.; 5) Crump et al. (2009)-- our rebuttal of Rory's letter

In addition there are two more papers which appeared in Risk Analysis and which detail the uncertainties further (Subramaniam et al. 2007, 2008). I can send these along if you need them.

The most significant uncertainty is the modeling of initiated cell birth and death rates for which there are no data. There are data (including that at low dose) for normal cell division rates, so Conolly et al. related initiated cell division rates to that of normal cells using a 2-parameter function. These parameters were determined by fitting the BBDR model predictions to the tumor incidence data in rats, and then assuming that the same function could be used for humans. Our sensitivity analysis of this issue showed that slight perturbations of these parameters (that were substantially smaller compared to the variability in the empirical normal cell division rates) could change human risk by more than 3-orders of magnitude, while not affecting the fit to the rat tumor incidence data in any appreciable way.

I will stop at this for now, and can continue further upon hearing from you.

(See attached file: NRC report Summary.docx)(See attached file: NRC Chap3.doc)(See attached file: Crump.Human.hchomodel.uncert_AnnOccHyg.2008.pdf)(See attached file: ConollyLetter.on.Crump.AOH.2009.pdf)(See attached file: Crump.Reply.to.Conolly_AOH.2009.pdf)

Best Regards,
Ravi

Ravi Subramaniam
Environmental Health Scientist
NCEA-Washington, ORD, EPA
N-7934, Two Potomac Yard, Crystal City
(703) 347-8606, (301) 515-2701 (alternate office)
